Thomas X White
Associate Vice President
Manufacturing and Quality Control
Scientific and Regulatory Affairs

PhRMA

March 31, 1999

Dockets Management Branch(HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 98D-0994; Draft Guidance for Industry on BACPAC I: Intermediates in Drug Substance Synthesis; Bulk Actives Post-approval Changes: Chemistry, Manufacturing and Controls (CMC)Documentation; Notice of Availability Appearing in the Federal Register of November 30, 1998 (63FR65793)

Dear Sir/Madam:

PhRMA comments submitted to the Docket for the subject draft guidance did not include one of the listed attachments. Three copies of an article entitled, "PhRMA Bulk Active Postapproval Changes (BACPAC) Decion Tree" are enclosed for incorporation into the Docket as attachments to the PhRMA comments delivered to the Docket on Tuesday, March 30, 1999.

I apologize for any inconvenience caused by the omission. Thank you for your assistance in this matter. If you have any questions, please contact me directly.

Sincerely,

Thomas X. White

Enclosures

98D-0994 SUP 1

PHARMACEUTICAL TECHNOLOGY®

PhRMA Bulk Active Postapproval Changes (BACPAC) Decision Tree

PhRMA Bulk Active Pharmaceutical Committee

For several years industry and FDA have reexamined the requirements for reporting postapproval changes. Recently, experts have held important discussions about the reporting requirements for postapproval changes in the manufacture of active pharmaceutical ingredients — bulk active postapproval changes (BACPAC). This article reflects the consensus position of PhRMA member companies with respect to such changes.

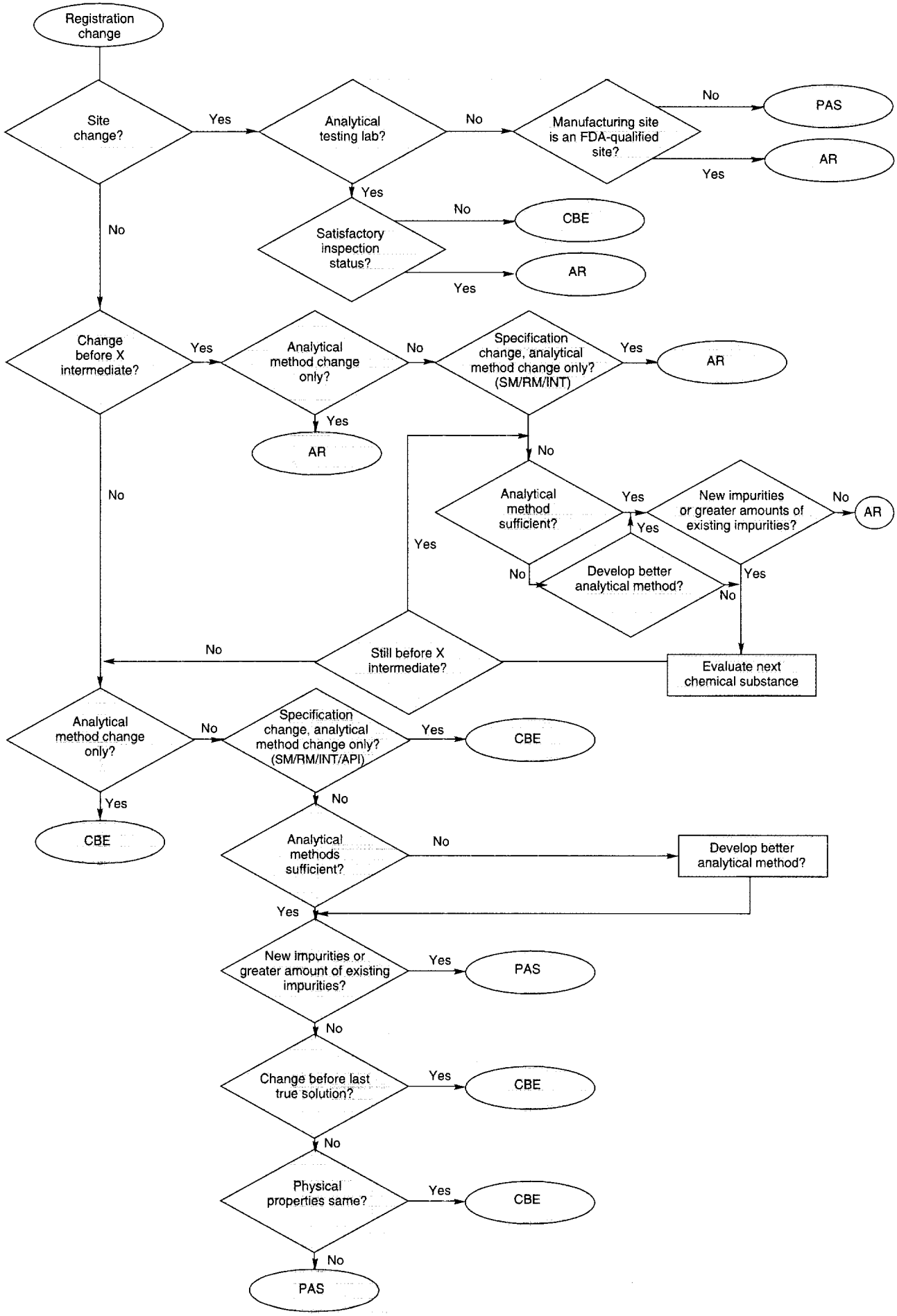
PhRMA BACPAC Work Group

Sean Brennan, Parke-Davis Division of Warner-Lambert Co.
Peter Begosh, SmithKline Beecham Pharmaceuticals
Chris Brooks, Novartis Pharmaceuticals Corp.
Betsy Fritschel, Johnson & Johnson
David Fry, Bristol-Myers Squibb Co.
Gerry Kirschner, Eli Lilly and Co. (retired)
Terrence Lambe, Pfizer Inc.
Lawrence Leatherman, Bristol-Myers Squibb Co.
Richard Lowenthal, Janssen Pharmaceutica
Michael Michailidis, Merck & Co., Inc.
John Mioduski, Hoffmann–La Roche Inc.
Rolland Pfund, Novartis Pharmaceuticals Corp.
Robert Poulton, SmithKline Beecham Pharmaceuticals
Bill Regan, Bristol-Myers Squibb Co.
David Ridge, Hoffmann–La Roche Inc.
Rick Saffee, Parke-Davis Division of Warner-Lambert Co.
Edward Smithwick, Eli Lilly and Co. (retired)
Joseph Timko, Pharmacia & Upjohn, Inc.
Lew Turano, Pfizer Inc.
Tom Van Laar, Searle
Jerry Walker, Pharmacia & Upjohn Inc.
Thomas X. White, PhRMA
*Jean Wyvratt, Merck & Co., Inc., chairman and corresponding author, tel. (732) 594-7174, fax (732) 594-1110, e-mail (jean_wyvratt@merck.com).

During the past several years industry and FDA have worked together to reexamine the requirements for reporting postapproval changes. The overall effort to reinvent government operations created the opportunity to refocus on regulatory relief. The first in the series of scale-up and postapproval changes (SUPAC-IR) set the stage and suggested methods for regulatory relief for immediate-release oral drug products. Since then regulatory agencies have initiated other documents covering postapproval changes. Recently, experts have held important discussions about the reporting requirements for postapproval changes in the manufacturing of active pharmaceutical ingredients — bulk active postapproval changes (BACPAC).

This article reflects the consensus position of PhRMA member companies with respect to changes in an approved registration for active pharmaceutical ingredients (also referred to as drug substances). A drug substance is typically a well-characterized molecule prepared by a unique sequence of chemical reactions. A drug product combines drug substances with inactive excipients in a dosage form (e.g., tablet, capsule, or suspension) and is prepared by standard operations. A drug substance is defined by its chemical structure and its associated chemical and physical properties, whereas the properties of a drug product are linked to its manufacturing process. The current article presents an approach for evaluating a manufacturing change by using a data-driven scientific comparison of material prepared in the absence of (pre-) and using (post-) the proposed change. This comparison focuses on the ability of analytical techniques to detect changes in the quality attributes of intermediates and drug substances. Comparing the results from analyses of material prepared pre- and postchange allows manufacturers to assess the effect of a given change. In assessing these changes, firms are concerned not only about the regulatory issues but more importantly about the safety, efficacy, and quality of their products.

The decision tree presented here is arranged from the perspective of supporting a change in the approved NDA regis-


Registration change
Site change?
Yes
Analytical testing lab?
No
Manufacturing site is an FDA-qualified site?
No
PAS
Yes
AR
Yes
Satisfactory inspection status?
No
CBE
Yes
AR
No
Change before X intermediate?
Yes
Analytical method change only?
No
Specification change, analytical method change only? (SM/RM/INT)
Yes
AR
Yes
AR
No
Analytical method sufficient?
Yes
New impurities or greater amounts of existing impurities?
No
AR
Yes
No
Develop better analytical method?
Yes
No
Yes
No
Still before X intermediate?
Evaluate next chemical substance
Analytical method change only?
No
Specification change, analytical method change only? (SM/RM/INT/API)
Yes
CBE
Yes
CBE
No
Analytical methods sufficient?
No
Develop better analytical method?
Yes
New impurities or greater amount of existing impurities?
Yes
PAS
No
Change before last true solution?
Yes
CBE
No
Physical properties same?
Yes
CBE
No
PAS

Definitions for decision tree

API	active pharmaceutical ingredient
FDA qualified site	currently manufacturing/testing an FDA-approved product/intermediate, which uses a similar process or technology, and has a current satisfactory GMP inspection by FDA or a governmental authority recognized by FDA
AR	annual report
CBE	changes being effected supplement
PAS	prior approval supplement
X intermediate	well-characterized, isolated intermediate which requires chemical bond formation/breaking to convert to drug substance, may be the last intermediate
SM/RM/INT	starting material/raw material/ intermediate
last true solution	the processing point at which the drug substance is completely dissolved for the last time

tration. The outcomes of the decision tree are regulatory reporting recommendations based on present postapproval filing mechanisms. Each change is correlated with the probability of affecting the drug substance and/or drug product. Those changes with a low probability of influencing the drug substance should be reported in annual reports (AR). Those with a high probability of impact should require prior approval supplements (PAS). Those in between require changes being effected (CBE) supplements.

The decision tree covers all processing steps in the preparation of drug substances produced by chemical synthesis, including chemical transformation of fermentation-derived substances. The changes include, but are not limited to, manufacturing site, materials used, equipment, scale, chemistry, processing operations, and testing methods. Although the specifics may be different for some operations such as fermentation or biotech drug substances, the overall approach is the same. Biologics that are not well characterized fall outside the scope of this decision tree because it is based on the use of analytical testing to show equivalence. Evaluating change in this manner (i.e., assessing the effect of change via a data-driven analysis) relies on analytical tools to evaluate impurity profiles and physical properties. The evaluation is also supported by a scientific understanding of the relevance of changes in various portions of a process based on the extensive experience with that process. GMP issues, validation, stability protocols, retest dating, and packaging are also outside the scope of this decision tree.

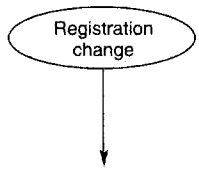
Imbedded within the decision tree is the concept of evaluating a material pre- and postchange. This evaluation depends on proper analytical methods as well as proper criteria. Depending on the specific change and good science, the proper criteria include established specifications and an evaluation of new impurities or greater amounts of existing impurities using ICH impurity guidelines. Criteria for physical properties may include established specifications as well as comparisons with previous process capabilities. Proper analytical methods include existing methods and additional appropriate methods needed to evaluate impurities and physical properties. For example, if a material's purity is determined by titration only, additional techniques are required to provide an impurity profile comparison.

As the decision tree indicates, the evaluation occurs as close as possible to the actual point of change, thus ensuring that the most meaningful data are evaluated. The data used to evaluate the change should be incorporated into any registration filing for that change.

ORGANIZATION

The decision tree can be divided into four major areas: the initial decision phase, changes involving site changes, changes before a demarcation point in the synthesis, and changes beyond that demarcation point in the synthesis. Each area has a consistent thought process. In general, changes can be evaluated within each area on a stand-alone basis. Some examples of change, however, must be evaluated in more than one area. In these cases each aspect should be independently evaluated with the most restrictive reporting requirement applied for a regulatory filing.

INITIAL DECISION

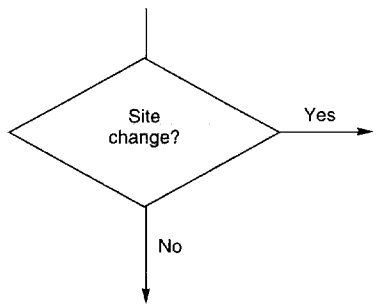


The starting point for the decision tree is the potentially difficult decision about the significance of a particular change. Existing regulations provide direction and requirements about when changes need to be reported for approved registrations. In fact, 21 *CFR* 314.70(a) begins with the following:

> Changes to an approved application. The applicant shall notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application.

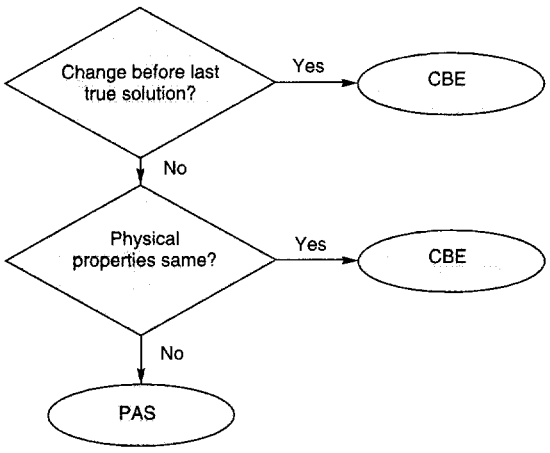
The first decision thus focuses on the change and the content of the approved application. If the change requires a modification to the registration, then the decision tree would apply. If the change does not require a change to the application, the decision tree would not apply for determining the reporting mechanism.

SITE CHANGE



For drug substance operations, sites are generally identified in registrations as manufacturing sites and/or control facilities.

Testing facilities generally are either specifically identified or are assumed to be part of the manufacturing site, which includes control facilities



a substance's physical properties. To do this, the manufacturer must determine if the change is before the processing point at which the drug substance is completely dissolved for the last time (referred to as the last true solution). Physical properties of the drug substance are established after the last true solution.

For a change that occurs after the *X* intermediate and before the last true solution, if appropriate analytical methods determine that there has been no negative effect on the impurity profile, the change has only a very low probability of influencing the drug substance. In this case, a CBE supplement would be sufficient without the need to wait for prior approval. If the change is after the last true solution but the analytical results show that the physical properties pre- and postchange are unchanged, then a CBE supplement is also consistent with the low probability of affecting the drug substance. If the physical properties are different, however, then the probability of influencing the drug product is high, and a PAS is appropriate.

SUMMARY

The PhRMA BACPAC decision tree outlines a unified approach that uses scientific assessment and historic experience for evaluating postapproval changes in drug substance manufacturing. The recommended regulatory reporting mechanisms reflect the major vs. minor impact of changes on the quality of the drug substance or an intermediate.

ARs and CBE supplements are suitable when manufacturing changes result in chemical substances that meet established specifications, along with impurity profile and physical property (only for changes after the last true solution) comparison criteria. Prior approval supplements are recommended only for changes that negatively affect the quality of the drug substance or for a manufacturing site change that necessitates a GMP inspection (i.e., the manufacturing site is not FDA qualified). This approach provides a consistent strategy that is based on the assessment of major vs. minor effects on the overall quality of the chemical substances resulting from bulk drug manufacturing changes, as opposed to attempting to categorize types of change themselves as major or minor.

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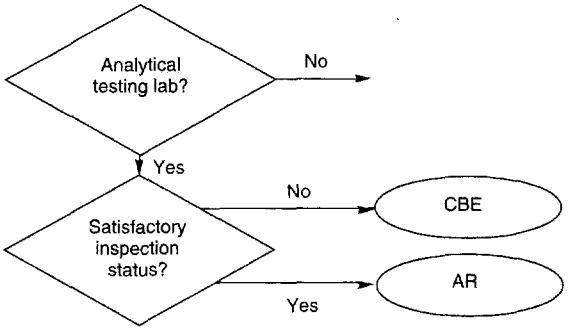
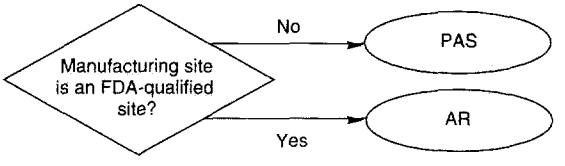
PhRMA

Pharmaceutical Research and Manufacturers of Amercia

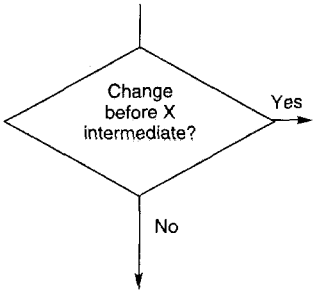


for raw materials, in-process testing, and drug substance release and/or stability. If the site change involves a change in the testing facility or the addition of another testing site, an AR would apply for testing laboratories with current satisfactory FDA inspection status, and a CBE would be appropriate for a testing laboratory without this status. GMP considerations of IQ/OQ and site qualification for the analytical methods being transferred would be independent of registration activities.

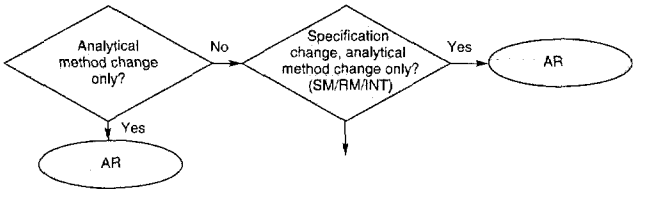


If the change involves a manufacturing site change, the decision centers around the status of the new site. An FDA-qualified site is one that currently manufactures an FDA-approved product or intermediate which uses a similar process or technology and has a current satisfactory GMP inspection (i.e., no regulatory action pending) by FDA or a governmental authority recognized by FDA. Assuming there are no other changes, the significance of the manufacturing site change is low, and the effect on the substance would be low. If this is the case, reporting can be done in an AR. This assumption includes equivalence of the process, equipment, materials, and quality systems. If these conditions are not met, then additional changes must be evaluated in other portions of the decision tree. If the new site is not FDA qualified, a PAS is required to ensure the opportunity for FDA compliance evaluation. In either case, data supporting such a change should be consistent with the processing step and the decision tree.

CHANGES MADE BEFORE AN *X* INTERMEDIATE

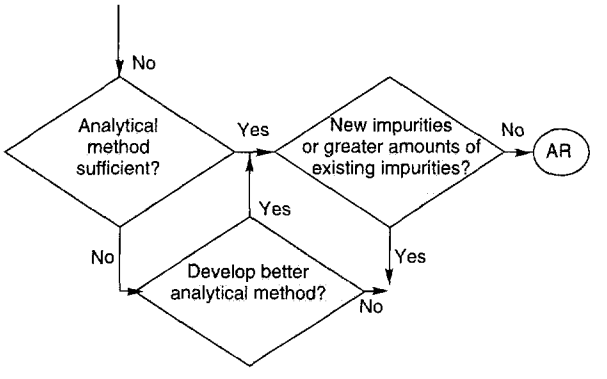


Experts generally agree that in a multistep chemical synthesis, changes made in early steps present a lower risk of affecting the drug substance than do changes made in late steps. For each synthesis there is an intermediate that represents the transition from early process steps to late process steps. Many groups have identified this intermediate by various terms, each with slightly different definitions, resulting in confusion and a lack of consensus. Rather than using an existing term, *X intermediate* will be employed to focus on the concept of the characteristics of that intermediate. The *X* intermediate is the last well-characterized, isolated intermediate before the formation of the active molecule (i.e., a molecule that requires chemical bond formation or breaking to form the final drug substance, i.e., not a salt). In a linear synthesis the *X* intermediate may be the last isolated intermediate before the drug substance. In a convergent synthesis — in which two isolated intermediates are being reacted together to form the drug substance molecule — both intermediates would be defined as *X* intermediates.

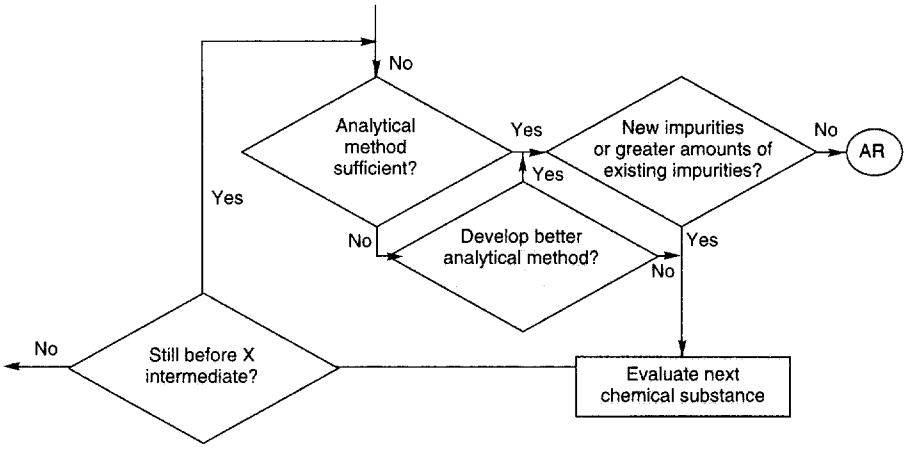


Bearing in mind this definition of an *X* intermediate, clearly one major category is that of changes before the *X* intermediate. There are two sets of changes within this category: one that comprises analytical method and/or specification changes only (i.e., no changes in the processing of any material) and the other dealing with actual changes in the operations. If there is only an analytical method change and all else remains consistent, the change would have low probability of affecting the drug substance (it is before an *X* intermediate) and would be consistent with AR requirements.

If a specification needs to be tightened or loosened for a starting material, raw material (including solvents), or intermediate, the decision must focus on the reason for the change. If the specification change is required only because a manufacturer is using a new analytical method that is equivalent to or better than the existing method without changing the material or process, then because this change is before the *X* intermediate the probability of affecting the drug substance is low and would be consistent with AR requirements. If the specification change is required because of an actual change in the operations, then further evaluations are necessary.



As discussed in the introduction, the fundamental advantage of evaluating changes in drug substance processing is the availability of many analytical tools. To that end, if there is an actual change of any type in the process, the primary decision depends on the adequacy of the analytical methods used to determine equivalence. Validated and suited for the intended

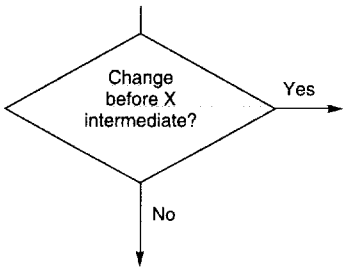


use, analytical methods (e.g., an assay method and impurity profile methods) should be available to evaluate the purity of the chemical substance. The impurity profile methods should have appropriate quantitation limits and should be specific not only for known impurities but also for potential new impurities based on the nature of the change. Methods that permit testing for specific solvents, reagents, or catalysts used in processing should also be available. If the analytical methods are scientifically sufficient, the evaluation compares the material produced with and without the change.

The decision focuses on new impurities or greater amounts of existing impurities. If there are no new impurities (organic, inorganic, residual solvents) greater than the ICH guidelines for qualifying impurities and if there are no greater amounts of existing impurities (based on process history), then the change would have a low probability of affecting the safety of the drug substance and would be consistent with AR requirements.

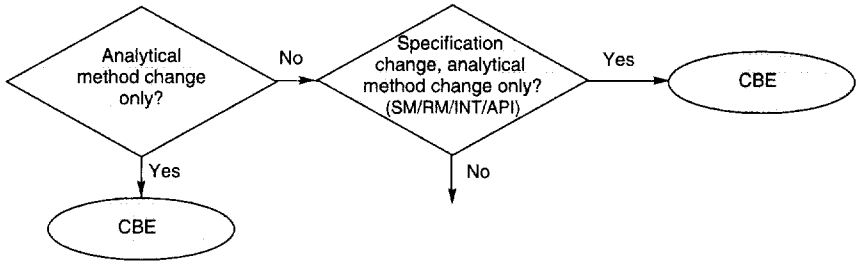
On the other hand, if there is a new impurity or if the amounts of existing impurities are greater than those specified in the ICH guidelines, then the material pre- and postchange is not equivalent at this processing stage. The significance of this fact must be evaluated by examining the next chemical substance. If this step is still before the *X* intermediate, then this approach is repeated at the next step in the synthesis. If it is not, then considerations proceed to the next stage of the decision tree.

CHANGES AFTER AN *X* INTERMEDIATE



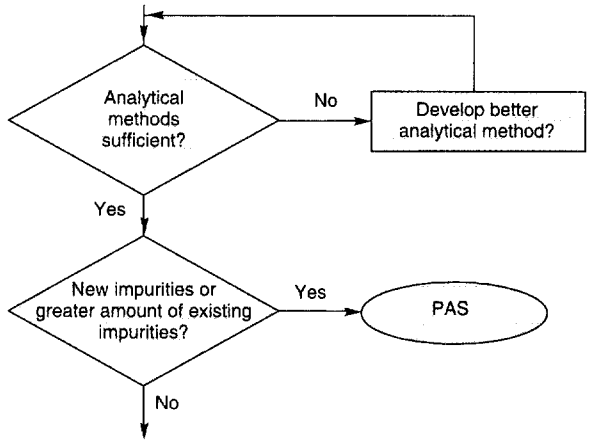
The item named, "Changes before *X* intermediate?" represents a significant break in the decision tree. Changes from the point of an isolated *X* intermediate through to the drug substance are viewed differently from the standpoint of the probability of affecting the impurity profile or physical properties of the drug substance.

As with changes before the *X* intermediate, changes can affect the analytical methods and/or specifications only (i.e., no changes in the production of the material) or can represent actual changes in the operations. If the change is an analytical method change only (i.e., use of an equivalent or better method) then the probability of affecting the drug substance is low. Because this change is beyond the *X* intermediate, a CBE supplement is recommended. An analogous situation would be a change to a specification of a material in this portion of the synthesis (starting material, raw material, intermediate, or even drug substance) in which case the specification change is driven only because of a change in the



analytical method without a change in the manufacturing operations. Reporting this type of change via a CBE supplement would be consistent with the low potential effect of this change.

On the other hand, if there is a processing change the manufacturer must address the question of impurities. As in the sections before the *X* intermediate portion of the decision tree, the manufacturer must examine the adequacy of the analytical methods for



existing and new impurities. Additional or improved analytical methods are necessary if the existing methods are inadequate. If the methods are scientifically acceptable, the company must evaluate the impurity profile while considering ICH guidelines. If there are new impurities or greater amounts of existing impurities, the change represents a high probability of affecting the drug substance. If the manufacturer decides to implement the change, reporting via a prior approval supplement (PAS) is consistent.

Even if the impurity profile change would lead to a PAS, a manufacturer may also need to assess the effect of the change on